Clinical Significance of Vascular Endothelial Growth Factor in Diagnosis of Hepatocellular Carcinoma Patients

Thesis

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الأهمية الإكلينيكية لمعامل نمو الخلايا المبطنة للأوعية الدموية فى تشخيص مرضى سرطان الكبد الأولى

رسالة

توطئة للحصول على درجة الماجستير

فى الباثولوجيا الإكلينكية والكيميائية

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Summary and Conclusion

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world **(El-Serag, 2002)** and the third most common cause of cancer related death **(Kaseb et al., 2009).** It results in 598,000 deaths per year worldwide **(Parkin et al., 2005)**.

Diagnosis of HCC depends on clinical evaluation, laboratory diagnosis, imaging techniques and histopathological techniques. The patient may be completely asymptomatic with no physical signs other than those of cirrhosis. So the laboratory markers of HCC are very important in early diagnosis for better prognosis ***(Kim et al., 2006).***

Any cause of liver disease that can result in cirrhosis should be considered a potential risk factor for HCC. The most common causes of cirrhosis, namely HBV, HCV and alcohol, are also the most common causes of HCC ***(Davis et al., 2008).***

The conventional and the most commonly used marker for HCC is alpha fetoprotein (AFP), but it has low specificity and unsatisfactory sensitivity in the diagnosis of early HCC. So there is need for supplementary markers for AFP to increase the sensitivity in early diagnosis of HCC as well as the specificity in differentiation between HCC and benign lesions ***(Kim et al., 2006).***

Contents

List of Abbreviations

ACTH	Adrenocorticotrophic hormone
AF	Aflatoxin
AFB_1	Aflatoxin B_1
AFP	Alpha fetoprotein
AFPIC	Alpha fetoprotein immunocomplex
AFU	Alpha- l - fucosidase
AJCC	American joint committee on cancer
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under curve
BCLC	Barcelona clinic liver cancer
CD	Cluster of differentiation
cDNA	Complementary DNA
CEA	Carcinoembryonic antigen
CECT	Contrast-enhanced helical computed tomography
CEUS	Contrast enhanced ultrasound
CLD	Chronic liver diseases
CLIP	Cancer of the liver Italian program
CT	Computerized tomography
CTAP	CT arterial portography
CTHA	CT hepatic arteriography
DCP	Des-gamma-carboxy-prothrombin
DN	Dysplastic nodules
DNA	Deoxyribonucleic acid
ELISA	Enzyme linked immunosorbant assay
FACS	Flowcytometry
FHCC	Fibrolamellar hepatocellular carcinoma
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
FNAB	Fine needle aspiration biopsy
GGT	Gamma-glutamyl transferase
GP73	Golgi protein 73
GPC3	Glypican 3
GST-Pi	Glutathione S-transferase-Pi
HBeAg	Hepatitis B envelop antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

HCC	Hepatocellular carcinoma
HCCR	Hepatocellular carcinoma receptor
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HIF	Hypoxia-inducible factor
HIF-lα	Hypoxia-inducible factor I-a
HIV	Human immunodeficiency virus
hTERT	Human telomerase reverse transcriptase
IGF-II	Insulin – like growth factor II
IHC	Immunohistochemical
IL-2R	Interleukin-2R
IL-8	Interleukin-8
INR	International normalized ratio
IQR	Inter-quartile range
kDa	Kilo dalton
LCA	Lens culinaris agglutinin
LDH	Lactate dehydrogenase
MDCT	Multidetector helical CT
MMP	Matrix metalloprotease
MPCT	Multiphasic helical CT
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
NAFLD	Nonalcoholic fatty liver disease
NCI	National cancer institute
NPV	Negative predictive value
NRP-l	Neuropilin-1
OPN	Osteopontin
PBS	Phosphate buffered saline
p-CEA	Polyclonal carcinoembryonic antigen
PCOS	Polycystic ovary syndrome
PCR	Polymerase chain reaction
PIGF	Placenta growth factor
PIVKA-II	Protein induced by vitamin k absence/antagonist-II
PPV	Positive predictive value
PST	Performance status test
PT	Prothrombin time
RA	Rheumatoid arthritis
RIA	Solid-phase Radioimmunoassay
RNA	Ribonucleic acid
ROC	Receiver operating characteristics
RT-PCR	Reverse transcriptase pcr

SCCA	Squamous cell carcinoma antigen
SCCAIC	Squamous Cell Carcinoma Antigen immune complex
SD	Standard deviation
SELDI-TOF MS	Surface-enhanced laser desorption/ionization-time of flight mass spectrometry
sGPC3	Soluble GPC3
SHF	Schistosomal hepatic fibrosis
TGF-B1	Transforming growth factor beta 1
TMB	Tetramethyl-Benzidine
TNM	Tumor- nodal- metastasis
TNM	Tumor-lymph node-metastasis
TSGF	Tumor-specific growth factor
US	Ultrasonography
USA	United States of America
VCAM-1	Vascular-cell adhesion molecules-1
VEGF	Vascular endothelial growth factor
VPF	Vascular permeability factor
χ^2	Chi-Squared test

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world **(El-Serag, 2002)** and the third most common cause of cancer related death **(Parkin et al., 2001 & Kaseb et al., 2009).** It results in 598,000 deaths per year worldwide **(Parkin et al., 2005)**. Its incidence is increasing worldwide ranging between 3 and 9% annually **(Velazquez et al., 2003).** More than 500,000 new cases are currently diagnosed yearly **(Llovet et al., 2003).**

There is considerable geographical variation in the incidence of HCC **(Parkin, 2006).** The rates of HCV in Egypt are among the highest in the world **(Arafa et al., 2005 and El-Gafaary et al., 2005)**. In Egypt, the annual proportion of HCC showed a significant rising trend from 4.7% in 1993 to 7.2% in 2002 **(El-Zayadi et al., 2005)**. HCC generally occurs in association with cirrhosis, particularly due to hepatitis C, hepatitis B, alcohol, hereditary hemochromatosis, and primary biliary cirrhosis **(Bruix and Sherman, 2005)**.

If HCC left untreated, liver cancer has a poor prognosis **(Jemal et al., 2006)**. Complete surgical resection and liver transplant are at present the only curative treatment options **(Schwartz et al., 2003)**. Unfortunately, the majority of patients with liver cancer are present with advanced unresectable disease so they are not surgical candidates **(Lopez et al., 2004 and Kaseb et al., 2009).** Hence, screening programs of patients

at risk, such as chronic carriers of hepatitis B and C represent attractive strategies for potential improvement of the outcome of HCC patients.

Currently, imaging techniques including ultrasonography, computed tomography scanning, and magnetic resonance are used for the diagnosis of HCCs. However, these techniques can not adequately differentiate benign hepatic lesions from HCC **(Befeler et al., 2002)**.

Therefore, it is very important to detect this disease and the recurrence at its earlier period. Serum tumor markers are the effective method for detecting hepatocellular carcinoma for a long time **(Zhou et al., 2006)**.

Serum alpha fetoprotein (AFP) is the most widely used tumor marker for diagnosis as well as surveillance of HCC **(Hsia et al., 2007 and Kaseb et al., 2009)**. However, AFP levels may be normal in up to 40% of patients with HCC, particularly during the early stages (low sensitivity). Furthermore elevated AFP levels may be seen in patients with cirrhosis or exacerbations of chronic hepatitis (low specificity) **(Wei et al., 2006)**.

Thus the identification of novel biochemical markers for HCC remains an important goal for many laboratories around the world **(Nakatsura et al., 2003)**.

Hepatocellular carcinoma (HCC) is a highly vascular tumor characterized by neovascularization and a high propensity for venous invasion **(Poon et al., 2001)**.

Vascular endothelial growth factor (VEGF) is the most potent directly acting angiogenic factor known so far, It is a soluble, homodimeric 34 - 42 kDa heparin-binding glycoprotein that specifically stimulates endothelial cell proliferation and enhances vascular permeability **(Poon et al., 2001)**.

VEGF promotes extravasation of plasma fibrinogen, leading to the formation of fibrin scaffolding that facilitates cell migration during invasion **(Dvorak et al., 1995 & Kaseb et al., 2009)**. As an endothelial growth factor, VEGF stimulates endothelial cell proliferation, thus inducing the budding of new blood vessels around the growing tumor masses **(Kaseb et al., 2009).**

Zhou et al., 2006 and **Kaseb et al., 2009** reported that serum VEGF levels were significantly elevated in HCC patients as compared with patients with benign liver lesions and normal controls. Also they reported that serum VEGF levels were not significantly different between the patients with benign liver lesions and normal controls.

Aim of the Work

The aim of the present study is to investigate the clinical utility of vascular endothelial growth factor (VEGF) in hepatocellular carcinoma (HCC) patients and comparing the results with those having chronic liver disease.